What is claimed is:

1. A pharmaceutical composition comprising a targeted enzyme (TE) and a pharmaceutically acceptable carrier, excipient or diluent, said TE exhibiting a catalytic activity and comprising:

    a) a substrate recognition site; and

    b) a targeting site that binds a target;

wherein

   i) the targeting site comprises a variant sequence that is derived from a variation-tolerant sequence of a corresponding pre-targeted enzyme,

   ii) the target is bound by the TE but not by the pre-targeted enzyme under like conditions,

   iii) the target is not an isolated monoclonal antibody, and

   iv) the variation-tolerant sequence is not in a protein binding domain of the pre-targeted enzyme.

2. A targeted enzyme exhibiting a catalytic activity, comprising:

    a) a substrate recognition site;

    b) a first targeting site that binds a first target; and

    c) a second targeting site that binds a second target,

wherein

   i) each targeting site comprises a variant sequence derived from variation-tolerant sequences of a corresponding pre-targeted enzyme, and

   ii) the affinity of the targeted enzyme for the first and second target is greater than the affinity of the pre-targeted enzyme for the first and second target under like conditions.

3. The targeted enzyme of Claim 2, wherein the first target and the second target are of a different identity.

4. The targeted enzyme of Claim 2, wherein the first target and second target bind targets of the same identity.

5. The targeted enzyme of Claim 2, wherein at least one of the targeting sites comprises two variant sequences.

6. The targeted enzyme of Claim 5, wherein at least one of the targeting sites comprises three variant sequences.

7. A targeted enzyme exhibiting a catalytic activity, comprising:

a) a substrate recognition site; and

b) a targeting site that binds a target,

wherein

i) the targeting site comprises two variant sequences derived from variation-tolerant sequences of a corresponding pre-targeted enzyme,

ii) the affinity of the targeted enzyme for the target is greater than the affinity of the pre-targeted enzyme for the target under like conditions, and

iii) the target is not an isolated monoclonal antibody.

8. A targeted enzyme exhibiting a catalytic activity, comprising:

a) a substrate recognition site; and

b) a targeting site that binds a target;

wherein

i) the targeting site comprises three variant sequences, wherein each of the variant sequences is derived from variation-tolerant sequences of a corresponding pre-targeted enzyme, and

ii) the affinity of the targeted enzyme for the target is greater than the affinity of the pre-targeted enzyme for the target under like conditions.

9. The pharmaceutical composition of Claim 1 wherein the targeted enzyme targeting site comprises two variant sequences targeted enzyme.

10. The pharmaceutical composition of Claim 1, wherein the targeted enzyme comprises two targeting sites.

11. The pharmaceutical composition of Claim 10, wherein the targeted enzyme targeting sites bind targets of different identities.

12. The pharmaceutical composition of Claim 1, wherein the targeted sequence variant sequence is between about 1 and about 50 amino acid residues.

13. The pharmaceutical composition of Claim 1, wherein the targeted sequence variant sequence is between about 3 and about 20 amino acid residues.

14. The pharmaceutical composition of Claim 1, wherein the targeted enzyme has a molecular weight of less than about 45,000 Daltons.

15. The pharmaceutical composition of Claim 1, wherein the targeted enzyme binds the target with a k_d of about 5 nM or less.

16. The pharmaceutical composition of Claim 1, wherein the targeted enzyme, while bound to target, exhibits a catalytic activity of greater than about 1% relative to the catalytic activity of the pre-targeted enzyme.

17. The targeted enzyme of one of Claims 1, 2, 7 or 8, wherein the pre-targeted enzyme is selected from the group consisting of: proteases, carboxypeptidases, β-lactamases, asparaginases, oxidases, hydrolases, lyases, lipases, cellulases, amylases, kinases, phosphatases, transferases, aldolases and reductases.

18. The pharmaceutical composition of Claim 1, wherein the target is a protein or a cell.

19. A nucleic acid encoding the targeted enzyme of Claim 1.

20. A plasmid comprising the nucleic acid of Claim 19.

21. A cell comprising the plasmid of Claim 20.

22. A composition comprising the targeted enzyme of Claim 1, 2, 7 or 8 and a pharmaceutically acceptable carrier, excipient or diluent.

23. A pharmaceutical composition comprising a targeted β-lactamase enzyme and a pharmaceutically acceptable carrier, excipient, or diluent, said enzyme comprising:

a) a substrate recognition site;

b) a targeting site that binds a target; and

c) a sequence KTXS at its substrate recognition site,

wherein

i) the targeting site comprises a variant sequence that is derived from a variation-tolerant sequence of a corresponding pre-targeted enzyme that does not bind the target,

ii) the target is bound by the targeted β-lactamase enzyme but not by the pre-targeted β-lactamase enzyme under like conditions, and

iii) the target is not an isolated monoclonal antibody.

24. A targeted β-lactamase enzyme exhibiting a catalytic activity, comprising:

a) a substrate recognition site;

b) a first targeting site that binds a first target;

c) a second targeting site that binds a second target; and

d) a sequence KTXS at its substrate recognition site,

wherein

i) each targeting site comprises a variant sequence derived from variation-tolerant sequences of a corresponding pre-targeted enzyme, and

ii) the affinity of the targeted enzyme for the first and second target is greater than the affinity of the pre-targeted enzyme for the first and second target under like conditions.

25. The targeted β-lactamase enzyme of Claim 24, wherein the first target and the second target are of a different identity.

26. The targeted β-lactamase enzyme of Claim 24, wherein the first target and second target bind targets of the same identity.

27. The targeted β-lactamase enzyme of Claim 24, wherein at least one of the targeting sites comprises two variant sequences.

28. The targeted β-lactamase enzyme of Claim 27, wherein at least one of the targeting sites comprises three variant sequences.

29. A targeted β-lactamase enzyme exhibiting a catalytic activity, comprising:

a) a substrate recognition site;

b) a targeting site that binds a target, and

c) a sequence KTXS at its substrate recognition site,

wherein

i) the targeting site comprises three variant sequences, wherein each of the variant sequences is derived from variation-tolerant sequences of a corresponding pre-targeted β-lactamase enzyme, and

ii) the affinity of the targeted β-lactamase enzyme for the target is greater than the affinity of the pre-targeted β-lactamase enzyme for the target under like conditions.

30. A targeted β-lactamase enzyme exhibiting a catalytic activity, comprising:

a) a substrate recognition site; and

b) a targeting site that binds a target, and

c) a sequence KTXS at its substrate recognition site,

wherein

i) the targeting site comprises two variant sequences, wherein each of the variant sequences is derived from variation-tolerant sequences of a corresponding pre-targeted β-lactamase enzyme,

ii) the affinity of the targeted β-lactamase enzyme for the target is greater than the affinity of the pre-targeted β-lactamase enzyme for the target, and

iii) the target is not an isolated monoclonal antibody.

31. The pharmaceutical composition of Claim 23, further comprising a sequence VHKTGSTG.

32. The pharmaceutical composition of Claim 23, wherein the targeting site comprises two variant sequences.

33. The pharmaceutical composition of Claim 23, wherein the targeted β-lactamase enzyme comprises two targeting sites.

34. The pharmaceutical composition of Claim 23, wherein the variation-tolerant sequence is selected from the group consisting of loop A, loop B, loop C, loop D and loop E.

35. A method of making a targeted enzyme, comprising:

a) generating a modified enzyme library by modifying a variation-tolerant sequence of an enzyme, wherein said enzyme comprises a substrate recognition site and has a catalytic activity, such that a multiplicity of modified enzymes is produced; and

b) selecting a first and second modified enzyme from the modified enzyme library that binds a target with an affinity that is greater than the affinity of the pre-modified enzyme for the target;

c) recombining a nucleic acid molecule that encodes the first modified enzyme and a nucleic acid that encodes the second modified enzyme so that a recombined nucleic acid molecule is formed that encodes a third modified enzyme; and

d) assaying the third modified enzyme for binding of the target with an affinity that is greater than the affinity of the pre-modified enzyme for the target under like conditions and for the catalytic activity while bound to the target.

36. The method of Claim 35, further comprising in step b) selecting a first and second modified enzyme that binds a target with an affinity that is greater than the affinity of the pre-modified enzyme for the target and has the catalytic activity.

37. A method of making a targeted enzyme, comprising:

a) generating a modified enzyme library by modifying a variation-tolerant sequence of an enzyme, wherein said enzyme comprises a substrate recognition site and has a catalytic activity, such that a multiplicity of modified enzymes is produced;

b) identifying a modified enzyme from the modified enzyme library that binds a target with an affinity that is greater than the affinity of the pre-modified enzyme for the target and has the catalytic activity while bound to the target,

c) repeating a cycle of a) and b) as necessary to identify a modified enzyme that binds the target with an affinity that is at least 100-fold greater than the affinity of the unmodified enzyme for the target,

wherein an enzyme modified in a further cycle of a) was identified in a previous cycle of b).